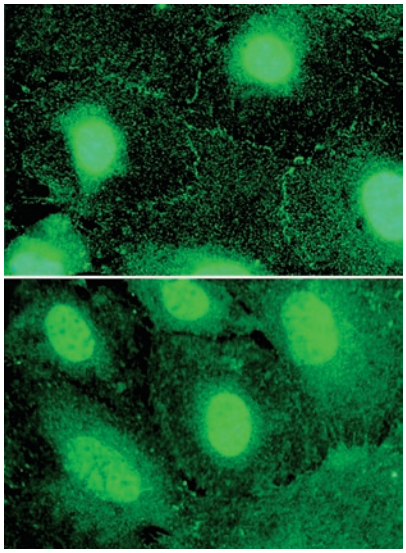
Kidney International (2008) **73,** 911–912. doi:10.1038/ki.2008.73

Epithelial-to-mesenchymal transition may be a pathway to podocyte dysfunction and proteinuria



Li *et al./Am J Pathol*

TGF-β1 inhibits P-cadherin expression in podocytes.

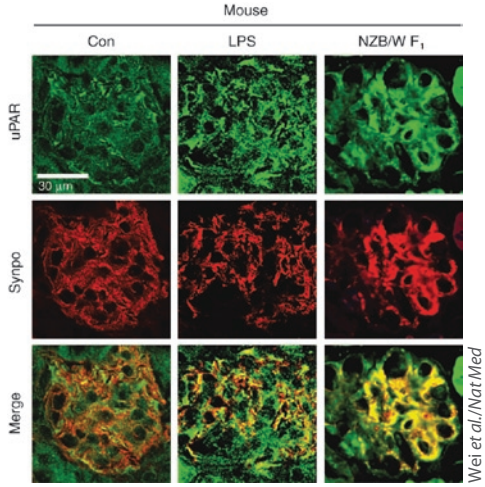
Podocyte dysfunction plays an essential role in the pathogenesis of proteinuria and glomerulosclerosis. However, the mechanism underlying podocyte dysfunction in many common forms of chronic kidney diseases remains poorly understood. Li *et al.* tested the hypothesis that podocytes may undergo epithelial-to-mesenchymal transition after injury. Conditionally immortalized mouse podocytes were incubated with transforming growth factor-β1 (TGF-β1), a potent fibrogenic cytokine that is upregulated in the diseased kidney. TGF-β1 suppressed the slit diaphragm-associated protein P-cadherin (Figure), zonula occludens-1, and nephrin, a change consistent with loss of the epithelial feature. Meanwhile, TGF-β1 induced the expression of the intermediate filament protein desmin and the interstitial matrix components fibronectin and collagen I. Furthermore, TGF-β1 promoted the expression and secretion of matrix metalloproteinase-9 by podocytes. Functionally, TGF-β1 increased albumin permeability across podocyte monolayers, as demonstrated by a paracellular albumin influx assay. The expression of Snail, a key transcriptional factor that has been implicated in the initiation of epithelial-to-mesenchymal transition, was induced by TGF-β1, and ectopic expression of Snail suppressed P-cadherin and nephrin in podocytes. *In vivo*, in addition to loss of nephrin and zonula occludens-1, mesenchymal markers such as desmin, fibroblast-specific protein-1, and matrix metalloproteinase-9 could be observed in glomerular podocytes of diabetic nephropathy. These results suggest that podocyte dedifferentiation and mesenchymal transition could be a potential pathway leading to their dysfunction, thereby playing a role in the genesis of proteinuria. (*Am J Pathol* 2008; **172**: 299–308; doi:10.2353/ajpath.2008.070057)

Marc De Broe

Physiological role for uPAR signaling in the regulation of kidney permeability

Podocyte dysfunction, represented by foot process effacement and proteinuria, is often the starting point for progressive kidney disease. Therapies aimed at the cellular level of the disease are currently not available. The urokinase receptor (uPAR) is required for the development of podocyte foot process effacement and proteinuria, which suggests that uPAR-inducible pathways are required for the remodeling of the filtration barrier. Wei *et al.* showed that induction of uPAR signaling in podocytes led to foot process effacement and urinary protein loss via a mechanism that includes lipid-dependent activation of αvβ3 integrin (Figure). Mice lacking uPAR (*Plaur*$^{-/-}$) were protected from lipopolysaccharide (LPS)-mediated proteinuria but developed disease after expression of a constitutively active β3 integrin. Gene transfer studies revealed a prerequisite of uPAR expression in podocytes, but not in endothelial cells, for the development of LPS-mediated proteinuria. Blockade of αvβ3 integrin reduced podocyte motility *in vitro* and lowered proteinuria in mice. These findings show a physiological role for uPAR signaling in the regulation of kidney permeability. Nonetheless, the role of uPAR in other glomerular cell types, as well as the potential interactions podocyte uPAR may have with other integrins and nonintegrins, needs to be studied further. (*Nat Med* 2008; **14**: 55–63; doi:10.1038/nm1696)

Marc De Broe



Wei *et al./Nat Med*

Induction of uPAR protein in podocytes in mouse models of proteinuria, as revealed by immunocytochemistry. NZB/W F_1, New Zealand black and white F_1 mice; Con, control glomeruli; Synpo, podocyte marker synaptopodin.

Entosis and cell death by invasion is a nonapoptotic process

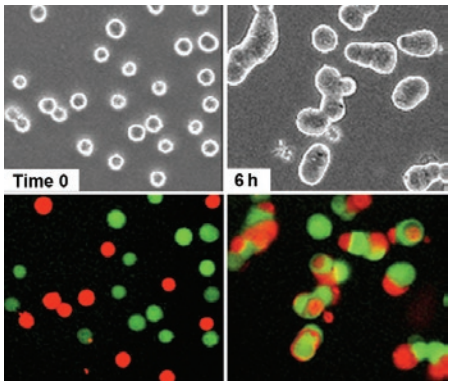


Figure 1 | Suspended cells internalize into their neighbors.

In multicellular organisms, cell proliferation and death are carefully coordinated to control the number and organization of cells in tissues and organs. Attachment to extracellular matrix is required for epithelial cells to suppress an apoptotic cell death program termed anoikis. Overholtzer *et al.* recently described a nonapoptotic cell death program in matrix-detached cells (that is, cells in suspension) that is initiated by a previously unrecognized and unusual process involving the invasion of one cell into another (Figure 1), leading to a transient state in which a live cell is contained within a neighboring host cell. The authors termed this cell internalization process entosis, after the Greek word *entos*, which means 'inside, into, or within.' While entosis and apoptosis both can result in the internalization of one cell inside another and death of the internalized cell, the mechanisms responsible for cell internalization are highly distinguishable. Unlike the phagocytic ingestion of apoptotic cells, cell internalization and death by entosis is not associated with caspase activation nor driven by phosphatidylserine exposure. Rather, it is dependent on adherens junctions and is driven by Rho and Rho-associated coil-forming kinase activity in internalizing cells, which is consistent with a cell invasion process rather than an engulfment process. Surprisingly, live internalized cells can also be released or undergo cell division (Figure 2), which highlights a further distinguishing aspect from cell engulfment in apoptosis; unlike dying cells that are cleared by phagocytosis, cells internalized by entosis are alive. Entosis likely explains the commonly observed 'cell-in-cell' cytological feature in human cancers and may represent an intrinsic tumor suppression mechanism for cells that are detached from extracellular matrix. The potential role of entosis in homeostatic and development processes remains to be explored. (*Cell* 2007; **131**: 966–979; doi:10.1016/j.cell.2007.10.040)

Juan Oliver

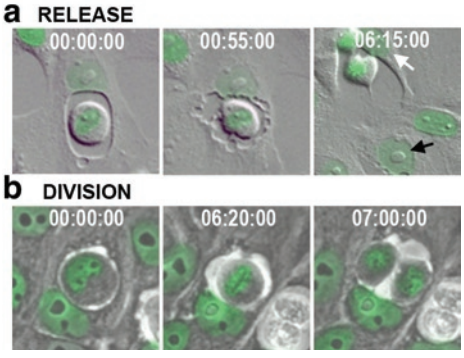


Figure 2 | Internalized cells can be released and can divide. (**a**) Internalized cell is released. White arrow marks previously internalized cell; black arrow marks outer cell. (**b**) Internalized cell divides.

Factor I required to develop MPGN2 in factor H deficiency

Membranoproliferative glomerulonephritis type II (MPGN2, also termed dense deposit disease) is characterized by the presence of intramembranous electron-dense material together with staining for C3, C5, and C9 along the glomerular basement membrane (GBM) in the absence of immunoglobulin. Uncontrolled activation of the alternative pathway of complement activation is an important feature of MPGN2. Spontaneous activation of C3 through the alternative pathway is regulated by two plasma proteins, factor H and factor I. Deficiency of either of these regulators results in uncontrolled C3 activation. While uncontrolled alternative pathway regulation and MPGN2 may occur in individuals with normal factor H and factor I activities, complete factor H deficiency results in spontaneous MPGN2. Despite the overwhelming evidence linking alternative pathway dysregulation and MPGN2, it is striking that MPGN2 has never been reported in individuals with factor I deficiency. To determine why individuals with uncontrolled C3 activation due to factor I deficiency do not develop MPGN2, Rose *et al.* generated factor I-deficient ($Cfi^{-/-}$) mice. These animals displayed uncontrolled alternative pathway activation as evidenced by reduced C3, factor B, and factor H levels but did not develop C3 deposition along the GBM or MPGN2. Hence, the renal phenotype of these mice differed significantly from the one reported previously in factor H-deficient ($Cfh^{-/-}$) mice. Remarkably, GBM C3 deposition did not occur, even in mice with combined deficiency of factors H and I ($Cfh^{-/-}Cfi^{-/-}$), despite the presence of uncontrolled alternative pathway activation. Analysis of plasma C3 activation fragments demonstrated that, in the absence of factor I, C3 circulated in the form of C3b with no evidence of formation of C3 metabolites. In contrast, in $Cfh^{-/-}$ mice, C3b cleavage fragments were detectable in plasma. Reconstitution of factor I in $Cfh^{-/-}Cfi^{-/-}$ mice precipitated GBM C3 deposition together with the concomitant appearance of C3b cleavage fragments in circulation. Renal transplant experiments confirmed that glomerular C3 deposition derives from the circulation in $Cfh^{-/-}$ animals. These elegant experiments demonstrate that factor I-mediated generation of activated C3 fragments in the circulation is critical for the development of MPGN2 associated with factor H deficiency. (*J Clin Invest* 2008; **118**: 608–618; doi:10.1172/JCI32525)

Juan Oliver